

**REMARKS**

Claims 1, 3-16 and 18-33 are pending in the application.

Claims 5, 6, 11, 12, 24, 25, 29, and 30 have been amended for further clarity by correcting a grammatical error to recite that "said CHO-Rluc cells are cultured in" medium.

Claim 16 has been amended to correct a typographical error by changing "said said" to "said cells."

Claims 1, 3-16 and 18-33 were rejected under 35 U.S.C. §103 for alleged obviousness over Evans *et al.*<sup>1</sup> in view of Yamashiro *et al.*<sup>2,3</sup> Applicant respectfully traverses because Applicants' prior arguments<sup>4</sup> in combination with Dr. Kohn's and the inventor Brown's attached Declarations (A) rebut the factual basis for the Examiner's conclusion, and (B) provide evidence of a long-felt but unsatisfied need in the art, that was met by the claimed invention.

**A. The Examiner's Factual Basis Is In Error as Demonstrated By Dr. Kohn's Declaration**

The Examiner's single argument in support of obviousness is that "the closest prior art is Evans *et al.* Evans *et al.*, discloses that in CHO-Rluc cells the levels of AMP generation were **directly correlated** to the level of gene expression detection by a luminometer. So there was a reasonable expectation that as PEG increased cAMP levels, this increase would lead to increased gene expression in CHO-RLuc cells."<sup>5</sup> However, the factual basis for the Examiner conclusion is in error as demonstrated by Dr. Kohn's Declaration.

Applicants first note that, based on Dr. Kohn's Curriculum Vitae that was previously mailed to the Office in this application on December 2, 2002, Dr. Kohn is an expert in the field of the invention, (1) with over **40 years** (from 1964 to present) of expertise, (2) with more than **388 peer-reviewed publications**, (3) is an inventor of several patents and patent application, (4) has served, and continues to serve, as a member on the editorial board of several notable scientific journals in fields related to the claimed invention. Therefore, Dr. Kohn is an expert in

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<sup>1</sup> Evans *et al.* (1999) "Development of a luminescent bioassay for thyroid stimulating antibodies," J. Clin. Endocrin. Metabolism 84(1)374-377.

<sup>2</sup> Yamashiro *et al.* (1999) "Mechanism of the Augmentative Effect of High Polyethylene Glycol (PEG) Concentrations on the Thyroid Stimulating Activity in TSAb-IgG Using a Porcine Thyroid Cell Assay," Endocrine Research 25:67-75.

<sup>3</sup> Final Office Action, page 2, item 2.

<sup>4</sup> Applicants incorporate all of their prior arguments, evidence, and Declarations.

<sup>5</sup> (Emphasis added) Final Office Action, page 2, item 2, last paragraph.

the field of the invention and is qualified to speak on the level of skill in the art, and on the state of the art at the time of filing the instant application.<sup>6</sup>

Dr. Kohn's Declaration provides data which squarely contradicts the Examiner's position by showing that reporter gene expression in CHO-Rluc cells is not mediated by cAMP, but rather is mediated by arachidonate/Ca/IP.<sup>7</sup> In addition, Dr. Kohn's Declaration shows that (1) the alleged correlation found in Evans *et al.* is the consequence of skewing the results by selecting a preponderance of TBII positive Graves' patient samples that have luciferase activity, while largely ignoring TBII negative Graves' patient samples with little, or no, luciferase activity, and (2) that, despite this skewing of results, the degree of alleged correlation between the released cAMP levels and gene expression levels in CHO-RLuc cells in these samples is low and insufficient to provide one of ordinary skill in the art with a reasonable expectation of success in predicting increased gene expression in response to PEG.<sup>8</sup> Dr. Kohn's factually based Declaration concluded that:

“the success of the instantly claimed methods was not obvious or predictable to me, nor could have been obvious or predictable to one of ordinary skill in the art, over Evans *et al.* in combination with Yamashiro *et al.* More particularly, in view of the above, it is my opinion that the combination of Evans *et al.*'s selection of a majority of TBII positive samples, together with the low degree of correlation between the level of released cAMP and the level of gene expression in Evans *et al.*'s CHO-Rluc cells in those samples, does not provide one of ordinary skill in the art with a reasonable expectation that increasing cAMP by using PEG would also result in increasing gene expression by using PEG.”<sup>9</sup>

Applicant submits that if the claimed invention was not obvious to Dr. Kohn, who is an authority in the relevant fields of the invention, then the invention cannot be obvious to one of “ordinary skill in the art.”

Since the Examiner's factual premise (*i.e.*, direct correlation between cAMP levels and gene expression levels) for concluding obviousness is incorrect, then a *prima facie* case of obviousness is improperly made. Because Dr. Kohn's Declaration (in combination with previously submitted evidence, Declarations, and arguments) demonstrates that the effect of PEG on cAMP as taught by Yamashiro *et al.* cannot reasonably be expected to predict a correlating effect of PEG on gene expression in Evans *et al.*'s CHO-Rluc cells, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103 over Evans *et al.* in view of Yamashiro *et al.*

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<sup>6</sup> Dr. Kohn's Curriculum Vitae, attached at Tab 1 to Applicant's response that was mailed to the Office on December 3, 2002.

<sup>7</sup> Dr. Kohn's Declaration, item 3.

<sup>8</sup> Dr. Kohn's Declaration, item 4.

<sup>9</sup> Dr. Kohn's Declaration, item 4.F.

**B. Nonobviousness is demonstrated by the Long-Felt Need And Failure Of Others As Demonstrated By Dr. Kohn's And Inventor Brown's Declarations**

Applicant further provides Dr. Kohn's and inventor Brown's Declarations to show that secondary considerations demonstrate the non-obviousness of the claimed methods. "The Federal Circuit has ... repeatedly emphasized the importance of the inquiry into secondary considerations, such as the commercial success of the invention and the prior failure of others, as the strongest precaution against judging an invention from the perspective of 20/20 hindsight."<sup>10</sup> Evidence that an invention satisfied a long-felt need which was not solved by others but satisfied by the invention is strong evidence that the invention was not obvious to those skilled in the art at the time the invention was made.<sup>11</sup>

As explained below, Dr. Kohn's Declaration demonstrates that (1) a long-felt and unsatisfied need existed in the art for a more accurate assay for detecting thyroid stimulating antibodies, and (2) the long-felt unsatisfied need was satisfied by the claimed methods.

**1. A Long-Felt And Unsatisfied Need Existed In The Art For A More Accurate Assay For Detecting Thyroid Stimulating Antibodies**

With respect to the period during which the need existed, the Court has said that the "long-felt need is analyzed as of the date the problem was identified and articulated, and there is evidence of efforts to solve that problem, not as of the date of the most pertinent prior art reference."<sup>12</sup> "Firsthand practical knowledge of unsolved needs in the art, by an expert, is evidence of the state of the art."<sup>13</sup>

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<sup>10</sup> Glaros v. H.H. Robertson co., 600 F.Supp. 342, 344, 224 USPQ 1037, 1038 (N.D. Ill. 1984), Aff'd, 797 F.2d 1564, 230 USPQ 393 (Fed. Cir. 1986).

<sup>11</sup> MPEP 716.04; See In re Tiffin, 443 F.2d , 394, 400, 170 USPQ 88 93-94 (CCPA 1971); see also Dow Chem. Co. v. America Cyanamid Co., 816 F.2d 617, 623, 2 USPQ2d 1350, 1355 (Fed. Cir. 1987); Rosemount, Inc. v. Beckman Instruments, Inc., 727 F.2d 1540, 1546, 221 USPQ 1, 7 (Fed. Cir. 1984) (finding invention satisfied long-felt need); E.L. Gore & Assocs., Inc. v. Garlock, Inc. 721 F.2d 1540, 1555, 220 USPQ 303, 314-15 (Fed. Cir. 1983) (same); Alco Standard Corp. v. Tennessee Valley Authority, 808 F.2d 1490, 1499-1500, 1USPQ2d 1337, 1344 (Fed. Cir. 1986), cert. denied, 483 U.S. 1052 (1987) (While "standing alone, the prior art provides significant support for the ... contention that the ... patent would have been obvious," evidence of secondary considerations, including the solution of a long-felt need, served to "establish that [the] invention appearing to have been obvious in light of the prior art was not.")

<sup>12</sup> MPEP 716.04, C2/A, citing Texas Instruments, Inc. v. Int'l Trade Comm'n, 988 F.2d 1165, 1179, 26 USPQ2d 1018, 1029 (Fed. Cir. 1993).

<sup>13</sup> In re Piasecki, 745 F.2d 1468, 1472, 223 USPQ 785 (Fed. Cir. 1984), citing In re McKenna, 40 CCPA 937, 203 F.2d 717, 97 USPQ 348 (CCPA 1953).

As discussed above, Dr. Kohn is undisputedly qualified to speak on the level of skill in the art, and on the state of the art at the time of filing the instant application. Dr. Kohn states that the need for an accurate assay for thyroid stimulating antibodies existed in the art since 1956, *i.e.*, for at least **42 years** before the filing date of the instant claims.<sup>14</sup> During those 42 years, several assays were developed, but none satisfied this long-standing need.<sup>15</sup> Indeed, until the advent of the claimed invention, the prior art recognized that the “major hurdle remains one of increasing the sensitivity of the available assays for TSHR-Ab so that their usefulness can be applied successfully to an even greater proportion of patients with Graves’ disease.”<sup>16</sup>

In view of the continuous efforts in the field over a period of at least 42 years to solve the problem, this failure was not due to the prior art’s a lack of interest or lack of appreciation of the invention’s potential. The continued existence of the problem in the art for at least 42 years created a demand for its correction, and it is reasonable to infer that the problem would not persist were the solution obvious, as the Examiner contended.

## **2. The Long-Felt Need Was Satisfied By The Instantly Claimed Methods**

Dr. Kohn’s Declaration demonstrates that the instantly claimed methods solved the problem in the art by increasing the accuracy of the detection of thyroid stimulating antibodies.<sup>17</sup>

Inventor Brown’s Declaration provides further evidence that the claimed methods solved a long-standing problem of inaccurate assays of thyroid stimulating antibodies in that the claimed methods received overwhelming peer recognition by 8 out of the 10 laboratories in the United States that specialize in bioassays for thyroid stimulating antibodies. The remaining 2 laboratories are considering switching to the instantly claimed methods.

Based on the above, and on Dr. Kohn’s and inventor Brown’s factually based opinions, “one of ordinary skill in the art would not have had a reasonable expectation of success in practicing the claimed methods based on the combined teachings of Evans *et al.* and Yamashiro *et al.*”<sup>18</sup>

In view of (1) the error in the factual basis for the Examiner’s finding of obviousness, (2) Applicant’s prior arguments, evidence and Declarations, and (3) the instant evidence that demonstrates that the claimed invention solved a long-standing problem in the art, the claims are

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<sup>14</sup> Dr. Kohn’s Declaration, item 2.

<sup>15</sup> *Id.*

<sup>16</sup> *Id.*

<sup>17</sup> Dr. Kohn’s Declaration, item 6.A.

<sup>18</sup> Dr. Kohn’s Declaration, item 6.B and inventor Brown’s Declaration, item 3.

**PATENT**Attorney Docket No. **DHI-03864**

non-obvious. Applicants therefore respectfully request that the rejection of the claims under 35 U.S.C. §103 over Evans *et al.* in view of Yamashiro *et al.* be withdrawn.

**CONCLUSION**

All grounds of rejection of the Office Action of November 14, 2003 having been addressed, the claims are in condition for allowance. Applicant encourages the Examiner to call the undersigned collect before beginning to draft a written communication, if any.

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**Maha A. Hamdan**  
Registration No. 43,655  
MEDLEN & CARROLL, LLP  
101 Howard Street, Suite 350  
San Francisco, California 94105  
(415) 904-6500